Absence of sclerostin adversely affects B cell survival.

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Public Summary:
Hematopoietic cell fate decisions are dependent on their localized microenvironmental niche. In the bone, endosteal osteoblasts have been shown to support hematopoietic stem cells (HSC) self-renewal, as demonstrated by transgenic and knockout mouse models in which osteoblast populations were increased or decreased. Sclerostin (Sost) is a secreted protein that is primarily expressed by fully mature osteocytes and acts on osteoblasts as a negative regulator of bone growth. Here, we investigated the role of Sost on hematopoiesis in the bone marrow niche. Increased osteoblast activity in sclerostin-knockout (Sost-/-) mice results in hypermineralized bones with small bone marrow cavities. As such, Sost-/- mice contain markedly reduced numbers of CD45+ hematopoietic cells in the bone marrow. Since hematopoietic stem cell activity is dependent on osteoblast function, we examined whether the hyperactive osteoblast activity in Sost-/- mice influences the numbers of hematopoietic stem cells, lymphoid progenitor cells and myeloid progenitor cells in the bone marrow. Surprisingly, no differences were observed in hematopoietic stem and progenitor cell frequency and cell number. However, we found the bone marrow of Sost-/- mice to be depleted of B cells, and this reduction can be attributed to premature apoptosis in B cell precursors in the BM. We also observed a significant decrease in CXCL12 expression in the bone marrow stroma in Sost-/- mice, consistent with their inability to adequately support B cell development. Transplantation of WT bone marrow into SOST-/- hosts resulted in aberrant B cell development, but the reciprocal Sost-/- to WT transplant was normal. Taken together, our results indicate that the B cell developmental defects in Sost-/- mice due to changes in the bone environment that indirectly affects the blood stem cells. Our studies demonstrate a novel role for Sost in the regulation of B cell development in the bone marrow.

Scientific Abstract:
Increased osteoblast activity in sclerostin-knockout (Sost(-/-)) mice results in generalized hyperostosis and bones with small bone marrow cavities due to hyperactive mineralizing osteoblast populations. Hematopoietic cell fate decisions are dependent on their local microenvironment, which contains osteoblast and stromal cell populations that support both hematopoietic stem cell quiescence and facilitate B cell development. In this study, we investigated whether high bone mass environments affect B cell development via the utilization of Sost(-/-) mice, a model of sclerosteosis. We found the bone marrow of Sost(-/-) mice to be specifically depleted of B cells, due to elevated apoptosis at all B cell developmental stages. In contrast, B cell function in the spleen was normal. Sost expression analysis confirmed that Sost is primarily expressed in osteocytes and is not expressed in any hematopoietic lineage, which indicated that the B cell defects in Sost(-/-) mice are non-cell autonomous and this was confirmed by transplantation of wildtype (WT) bone marrow into lethally irradiated Sost(-/-) recipients. WT-->Sost(-/-) chimeras displayed a reduction in B cells, whereas reciprocal Sost(-/-) -->WT chimeras did not, supporting the idea that the Sost(-/-) bone environment cannot fully support normal B cell development. Expression of the pre-B cell growth stimulating factor, Cxcl12, was significantly lower in bone marrow stromal cells of Sost(-/-) mice while the Wnt target genes Lef-1 and Ccnd1 remained unchanged in B cells. Taken together, these results demonstrate a novel role for Sost in the regulation of bone marrow environments that support B cells. (c) 2012 American Society for Bone and Mineral Research.